

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

14.
REC'D 30 MAR 2001

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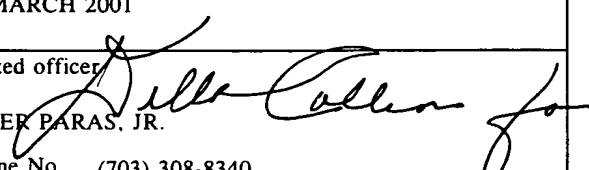
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Applicant's or agent's file reference 06727/008WO2	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US00/00264	International filing date (day/month/year) 06 JANUARY 2000	Priority date (day/month/year) 06 JANUARY 1999
International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet.		
Applicant ATLANTIC BIOPHARMACEUTICALS, INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets.
☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).
 These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 07 JULY 2000	Date of completion of this report 11 MARCH 2001
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer  PETER PARAS, JR.
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US00/00264

I. Basis of the report

1. With regard to the elements of the international application:*

☒ the international application as originally filed☒ the description:pages 1-21, as originally filedpages NONE, filed with the demandpages NONE, filed with the letter of _____☒ the claims:pages 22-26, as originally filedpages NONE, as amended (together with any statement) under Article 19pages NONE, filed with the demandpages NONE, filed with the letter of _____☒ the drawings:pages 1-4, as originally filedpages NONE, filed with the demandpages NONE, filed with the letter of _____☒ the sequence listing part of the description:pages NONE, as originally filedpages NONE, filed with the demandpages NONE, filed with the letter of _____2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).☐ the language of publication of the international application (under Rule 48.3(b)).☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:☐ contained in the international application in printed form.☐ filed together with the international application in computer readable form.☐ furnished subsequently to this Authority in written form.☐ furnished subsequently to this Authority in computer readable form.☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.4. ☒ The amendments have resulted in the cancellation of:☒ the description, pages NONE☒ the claims, Nos. NONE☒ the drawings, sheets/fig NONE5. ☐ This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

**Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

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V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. statement**

Novelty (N)	Claims	<u>1-20</u>	YES
	Claims	<u>NONE</u>	NO
Inventive Step (IS)	Claims	<u>NONE</u>	YES
	Claims	<u>1-20</u>	NO
Industrial Applicability (IA)	Claims	<u>1-20</u>	YES
	Claims	<u>NONE</u>	NO

2. citations and explanations (Rule 70.7)

Claims 1-17 lack an inventive step under PCT Article 33(3) as being obvious over Koyama in view of Tamaoki. Koyama teaches the creation of transgenic mice that express human alpha-fetoprotein. Tamaoki teaches the expression of genes in a variety of tissue types. Tamaoki teach the expression of human alpha-fetoprotein in vitro. In view of the fact that it is routine in the art to express a protein of interest in various tissues and body fluids of transgenic animals it would have been obvious to express human alpha-fetoprotein in the milk or urine of a transgenic animal, particularly a cow, sheep, or goat such that the specified body fluid may be collected and the recombinant human alpha-fetoprotein extracted.

Claims 18-20 lack an inventive step under PCT Article 33(3) as being obvious over the prior art as applied in the immediately preceding paragraph and further in view of Murgita. Murgita teaches the administration of recombinant human alpha-fetoprotein to treat cancer or suppress the proliferation of bone marrow in a mammal. In view of the fact that human alpha-fetoprotein can be used to treat cancer it would have been obvious to use large mammals such as cows, sheep, or goats as bioreactors to produce recombinant alpha-fetoprotein in their milk or urine.

----- NEW CITATIONS -----
NONE

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The description is objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 5 because it fails to contain an adequate written description of any and all transgenic non-human mammals that express hAFP. The description is inadequate because: Applicants do not appear to be in possession of the invention as reduction to practice has not been demonstrated. It would not be possible to envision the detailed chemical structure of any and all transgenic non-human mammals comprising a transgene which comprises a nucleotide sequence encoding hAFP and any corresponding phenotype resulting from transgene expression.

The description is objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 5 because it fails to adequately enable practice of the claimed invention because: the claimed transgenic non-human mammals have been contemplated in prophetic terms only. The art of transgenics is unpredictable with regard to transgene expression and a corresponding phenotype resulting from transgene expression. The specification does not provide any working examples that correlate transgene expression with a phenotype in any transgenic non-human mammal, particularly production of hAFP in the urine or milk of said transgenic mammal.

The description is objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 5 because it fails to adequately enable practice of the claimed invention because: the claimed methods of treatment comprising administration of hAFP to a patient are not supported by the specification. The art of treatment of patient by administration of a polypeptide is unpredictable. The specification does not provide any working examples that demonstrate a correlation between administration of hAFP with a therapeutic effect in a patient. As the claims are directed to a method of treatment in a patient the appears to be no other reason for using such a method other than to provide a therapeutic benefit.

Claims 1-2 are objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because the claims are indefinite for the following reason(s): the term "substantially pure" is a relative term that is not defined by either the claims or the specification. It is not clear exactly how pure a "substantially pure nucleic acid molecule" is when compared to any nucleic acid molecule. The metes and bounds of "substantially pure" can not be determined from the claim as written.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US00/00264

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

CLASSIFICATION:

The International Patent Classification (IPC) and/or the National classification are as listed below:

IPC(7): A01K 67/00, 67/033, 67/027; C12N 5/00, 5/02; C07K 1/00; A61K 39/00 and US Cl.: 800/3, 14; 435/325; 530/350; 424/277.1



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : A01K 67/00, 67/033, 67/027, C12N 5/00, 5/02, C07K 1/00, A61K 39/00	A3	(11) International Publication Number: WO 00/40693 (43) International Publication Date: 13 July 2000 (13.07.00)
(21) International Application Number: PCT/US00/00264 (22) International Filing Date: 6 January 2000 (06.01.00) (30) Priority Data: 60/114,995 6 January 1999 (06.01.99) US (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 60/114,995 (CIP) Filed on 6 January 1999 (06.01.99) (71) Applicant (for all designated States except US): ATLANTIC BIOPHARMACEUTICALS, INC. [US/US]; 50 Church Street, Cambridge, MA 02138 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): LINDSAY, Stace [US/US]; 8 Cypress Street, Cambridge, MA 02140 (US). MULROY, Robert [US/US]; 19 Hilliard Street, Cambridge, MA 02138 (US). SEMENIUK, Daniel [US/US]; 1860 Thousand Oaks Lane, Lawrenceville, GA 30043 (US). (74) Agent: CLARK, Paul, T.; Clark & Elbing LLP, 176 Federal Street, Boston, MA 02110-2214 (US).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> (88) Date of publication of the international search report: 28 September 2000 (28.09.00)
(54) Title: EXPRESSION OF SECRETED HUMAN ALPHA-FETOPROTEIN IN TRANSGENIC ANIMALS		
(57) Abstract The invention features a process of expressing secreted recombinant human alpha-fetoprotein (rHuAFP) in the milk or urine of transgenic mammals.		

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AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
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DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/00264

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : Please See Extra Sheet.

US CL : 800/3, 14; 435/325; 530/350; 424/277.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 800/3, 14; 435/325; 530/350; 424/277.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

MEDLINE, BIOSIS, EMBASE, SCISEARCH, CAPLUS, WEST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BENNETT et al. Similarity Between Natural and Recombinant Human Alpha-Fetoprotein as Inhibitors of Estrogen-Dependent Breast Cancer Growth. Breast Cancer Research and Treatment. September 1992. Vol. 45. No. 2. pages 169-179, especially page 175.	14,16, 18-19
Y	KOYAMA et al. Lectin Affinity Electrophoretic Demonstration of Tissue Specificity and Malignant Alteration of Human α -Fetoprotein Isoforms Produced in Transgenic Mice. Biochemical and Biophysical Research Communications. June 1996. Vol. 223. No. 3. pages 757-761, especially page 758.	14,16, 18-19



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

17 MARCH 2000

Date of mailing of the international search report

03 JUL 2000

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/00264

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DUDICH et al. Growth-Regulative Activity of Human Alpha-Fetoprotein for Different Types of Tumor and Normal Cells. Tumor Biology. January-February 1998. Vol. 19. No. 1. pages 30-40, especially page 36.	14,16, 18-20
A	Database SCISEARCH, Accession No. 1999:701362, BIRRER et al. 'The Immunology of Alphafetoprotein.' Abstract, Journal of Tumor Marker Oncology. Fall 1999. Vol. 14. No. 3. pages 55-62, see entire document.	1-20
Y, E	US 6,013,857 A (DEBOER et al) 11 January 2000 (11.01.00), see columns 6-7.	1-3,5-7, 10-11, 14-15
Y	WO 96/22787 A1 (MURGITA et al) 01 August 1996(01.08.96), especially pages 1-4.	14,16, 18-20
Y	US 5,766,884 A (TOWNES et al) 16 June 1998(16.06.98), see column 15, lines 5-55.	1-17
Y	US 5,843,776 A (TAMAOKI et al) 01 December 1998(01.12.98), see columns 5-6.	1-17

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/00264

A. CLASSIFICATION OF SUBJECT MATTER:

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